JAPANESE ENCEPHALITIS (JE) VACCINE

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ACIP JE Vaccine Work Group objectives

- Review newly available safety and immunogenicity data for JE vaccine
- Review epidemiology and risk of JE in travelers
- Review ACIP recommendations for use of JE vaccine in consideration of updated data
- Update MMWR Recommendations and Reports

Today's JE vaccine presentations

- GRADE for inactivated Vero cell culture-derived JE vaccine (Susan Hills, CDC)
- Background to comparative analysis of JE vaccination strategies (Marc Fischer, CDC)
- Comparative analysis of JE vaccination strategies (Martin Meltzer, CDC)
- Summary and conclusions (Susan Hills, CDC)

GRADE for inactivated Vero cell culture-derived JE vaccine (JE-VC)

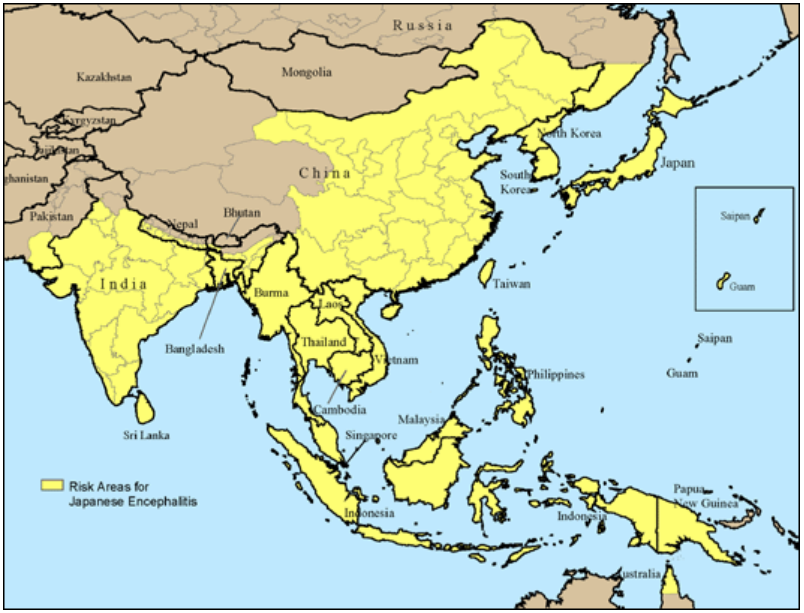
Dr Susan Hills, MBBS, MTH
Arboviral Diseases Branch
Division of Vector-Borne Diseases
Fort Collins, Colorado

June 21, 2018

Introduction and key issues

Japanese encephalitis (JE)

- Caused by a mosquito-borne flavivirus
- Occurs in most of Asia and Western Pacific
- Leading vaccine-preventable cause of encephalitis in Asia



JE virus infections in humans

- Most infections are asymptomatic
  - <1% infected people develop neurologic disease
- Clinical disease is often severe
  - 20%–30% case fatality
  - 30%–50% of survivors have sequelae
- No antiviral therapy; only supportive care

Vaughn DW. Epidemiol Rev 1992.

JE epidemiology in endemic countries

- Estimated 68,000 disease cases annually in Asia
- Overall incidence 1.8 per 100 000 population
- Highest risk in rural agricultural areas
- National vaccination programs in some endemic countries

Campbell GL. Bull World Health Organ 2011.

JE among travelers from non-endemic areas

- Risk of JE for most travelers is very low but varies based on travel destination, duration, season, and activities
- Overall incidence estimated <1 case per million travelers
- JE vaccine first licensed in the United States in 1992
- From 1992–2017, 12 JE cases reported among US travelers or expatriates

Hills SL. CDC Yellow Book 2018.

JE-VC (Ixiaro)

- Manufactured by Valneva Austria GmbH
- Only JE vaccine licensed and available in the US
- Licensed for
  - Adults aged ≥17 years in 2009
  - Children aged 2 months through 16 years in 2013
- Primary series: 2 doses administered 28 days apart
- Approximately $600 for 2-dose primary series

JE-VC efficacy and correlate of protection

- No efficacy data for JE-VC
  - Availability of several effective JE vaccines in Asia made a comparative efficacy trial difficult
- Established immunologic correlate of protection
  - JE virus 50% plaque reduction neutralization test ($PRNT_{50}$) titer ≥10

Hombach J. Vaccine 2005; Markoff L. Vaccine 2000.

JE-VC licensure

- Compared to licensed mouse brain-derived JE vaccine (JE-MB)
  - JE-MB had 91% efficacy in randomized controlled trial in >65,000 children in Thailand in 1984–86
  - Neutralizing antibody response to JE-VC non-inferior to JE-MB
- ≥95% seroprotection rates for JE-VC recipients in trials
- Good safety profile in pre-licensure studies
- Since 2009, >1 million doses distributed in U.S.

Hoke CH. N Engl J Med 1988; Tauber E. Lancet 2007; Tauber E. J Infect Dis 2008.

ACIP recommendations for use of JE-VC

2009:	Approved recommendations for primary series in adults
2011:	Approved recommendations for booster dose in adults
2013:	GRADE presented for use of JE-VC in child travelers
	Approved recommendations for primary series in children

GRADE evidence for JE-VC

GRADE rationale

- Routine review of recommendations in light of newly available safety and immunogenicity data since previous recommendations approved and published

Policy question

- Should JE-VC be recommended for use in persons aged ≥2 months at risk of travel-related exposure to JE virus?
  - Population: Persons aged ≥2 months traveling to JE risk areas
  - Intervention: JE-VC administered as a 2-dose primary series
  - Comparison: No JE vaccine recommended

Ranking and inclusion of outcome measures

	Importance	Data available	Include in evidence profile
Benefits			
Vaccine efficacy to prevent JE	Critical	No	--
Seroprotection at 1 month	Critical	Yes	Yes
Seroprotection at 6 months	Critical	Yes	Yes
Harms			
Serious adverse events	Critical	Yes	Yes
Adverse events of special interest	Critical	Yes	Yes
Injection site reactions	Important	Yes	No
Interference with other vaccines	Important	Yes	No

Evidence retrieval: search strategy

- Systematic search and review of published literature
- Searched Medline, Embase, CINAHL, and Cochrane Library databases for papers in any language
- Used keywords
  - Japanese encephalitis AND
  - Vaccine AND
  - IXIARO or JESPECT or IC51 or JEEV or Vero or Purified inactivated
- Title and abstract reviewed to identify relevant articles
  - If no abstract, paper reviewed

Search results

- Identified 21 studies that reported primary data relevant to the critical outcome measures
- Reviewed unpublished data
  - VAERS reports for JE-VC administered from May 2012–April 2016 in the United States or U.S. military personnel
  - Post-marketing adverse event surveillance among US military personnel using Defense Medical Surveillance System
  - Two clinical trails (one each in children and adults) of similar inactivated Vero cell culture-derived JE vaccine from India

Seroprotection at 1 month after primary series of JE-VC or comparator JE vaccine in RCTs

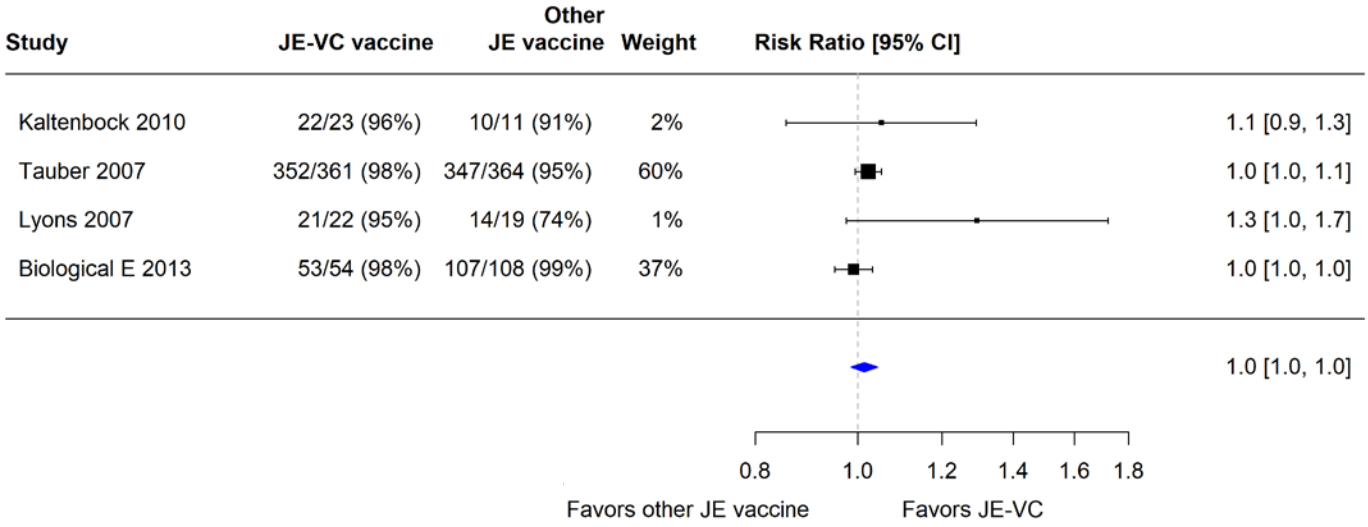
			PRNT50 titer ≥10	
Sites	Type	Age (yrs)	JE-VC	Other JE vaccine
India	RCT	1–2	22/23 (96%)	10/11 (91%)
US/Eur	RCT	≥18	352/361 (98%)	347/364 (95%)
US	RCT	18–49	21/22 (95%)	14/19 (74%)
India	RCT	18–49	53/54 (98%)	107/108 (99%)

Seroprotection at 1 month after primary series of JE-VC or comparator JE vaccine, observational

			PRNT50 titer ≥10	
Sites	Type	Age (yrs)	JE-VC	Other JE vaccine
Philippines	Obs*	0.2–17	384/385 (99%)	-- --
US/Eur/Aus	Obs	0.2–17	62/62 (100%)	-- --
Eur	Obs*	≥18	110/113 (97%)	-- --
Eur	Obs*	≥18	126/127 (99%)	-- --
US	Obs	≥18	88/92 (96%)	-- --
Eur	Obs	≥18	30/31 (97%)	13/15 (87%)
Eur	Obs*	18–65	206/206 (100%)	-- --
Eur	Obs	64–83	128/197 (65%)	-- --

*RCTs with no comparative immunogenicity data

Pooled risk ratios for seroprotection at 1 month after a primary series of JE-VC or comparator vaccine in RCTs*



*Risk ratio = Proportion seroprotected in JE-VC group / Proportion seroprotected in other JE vaccine group

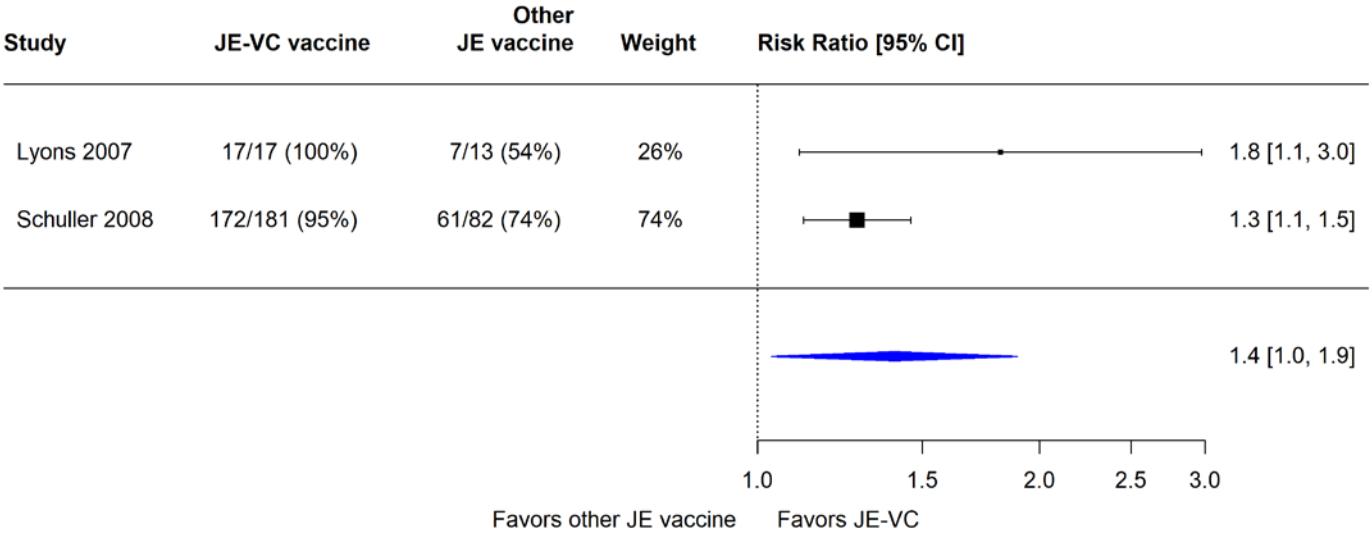
Seroprotection at 5–6 months after a primary series of JE-VC or comparator JE vaccine*

			PRNT50 titer ≥10	
Sites	Type	Age (yrs)	JE-VC	Other JE vaccine
US	RCT	18–49	17/17 (100%)	7/13 (54%)
Eur	RCT	≥18	172/181 (95%)	61/82 (74%)
Philippines	Obs†	0.2–17	358/389 (92%)	-- --
US/Eur/Aus	Obs	0.2–17	31/34 (91%)	-- --
Eur	Obs	≥18	96/116 (83%)	-- --
Eur	Obs†	18–65	190/204 (93%)	-- --

*5 mos after 2-dose primary series in adults; 6 mos after 2-doses in children

†RCT with no comparative immunogenicity data

Pooled risk ratios for seroprotection at 5–6 months after a primary series of JE-VC or comparator vaccine in RCTs*



*Risk ratio = Proportion seroprotected in JE-VC group / Proportion seroprotected in other JE vaccine group

Serious adverse events reported within 1 month after either dose of JE-VC or control vaccine, RCTs

			Serious adverse events	
Sites	Type	Age (yrs)	JE-VC	Control vaccine
India	RCT	1–2	0/48 (0)	0/12 (0)
Philippines	RCT	0.2–17	6/1411 (<1%)	5/458 (1%)
US/Eur	RCT	≥18	1/428 (<1%)	0/435 (0)
US/Eur/Aus	RCT	≥18	10/1993 (<1%)	6/657 (1%)
US	RCT	18–49	0/24 (0)	0/21 (0)
India	RCT	18–49	0/54 (0)	0/108 (0)
Eur	RCT	≥18	1/127 (1%)	0/65 (0)
Eur	RCT	18–65	5/56 (9%)	1/220 (<1%)

Serious adverse events reported within 1 month after either dose of JE-VC in observational studies

			Serious adverse events			
Sites	Type	Age (yrs)	JE-VC		Control vaccine	
US/Eur/Aus	Obs	0.2–17	0/100	(0)	--	--
Eur	Obs*	≥18	0/125	(0)	--	--
US	Obs	≥18	0/123	(0)	--	--
Eur	Obs	64–83	5/200	(3%)	--	--

*RCT with no comparative immunogenicity data

Serious adverse events reported within 6–7 months after first dose of JE-VC or control vaccine

			Serious adverse events	
Sites	Type	Age (yrs)	JE-VC	Control vaccine
Philippines	RCT	0.2–17	23/1411 (2%)	11/458 (2%)
US/Eur/Aus	RCT	≥18	38/3558 (1%)	16/1092 (1%)
US/Eur/Aus	Obs	0.2–17	3/100 (3%)	-- --
Eur	Obs	64–83 yr	8/200 (4%)	-- --

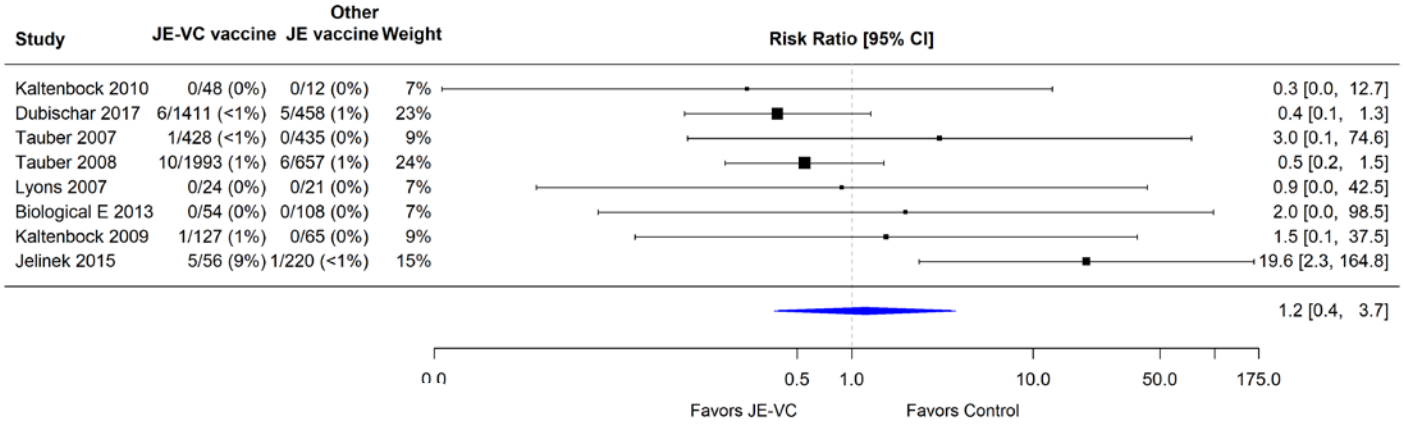
Serious adverse events reported through post-marketing surveillance

Countries	Reporting period	Doses distributed	Serious adverse events	
			No.	Rate†
US/Eur/Aus	Apr 2009–Mar 2010	246,687	4	1.6
US	May 2009–Apr 2012	275,848	5	1.8
US	May 2012–Apr 2016	802,229	9	1.1
US	Nov 2011–Aug 2014	145*	0	0

*Doses administered

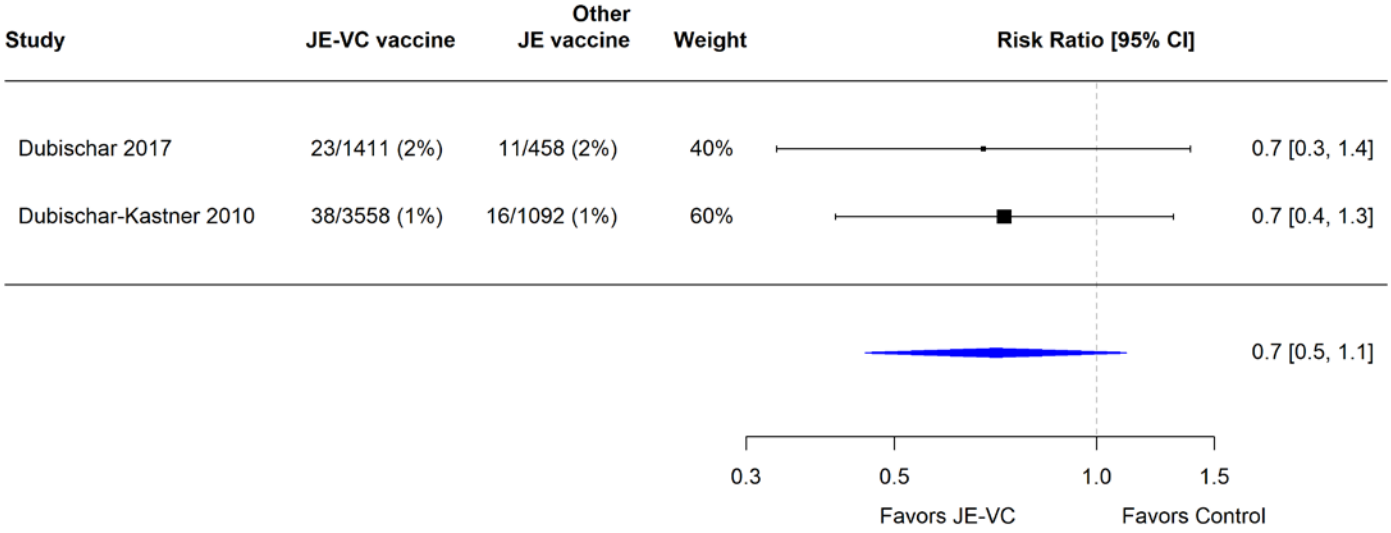
†Per 100,000 doses distributed; similar to or lower than rates for HPV, pneumococcal polysaccharide, yellow fever, and herpes zoster vaccines

Pooled risk ratios for serious adverse events within 1 month after either dose of JE-VC or control vaccine in RCTs*



*Risk ratio = Proportion with the adverse event in JE-VC group / Proportion with the adverse event in control group

Pooled risk ratios for serious adverse events within 6-7 months after either dose of JE-VC or control vaccine in RCTs*



*Risk ratio = Proportion with the adverse event in JE-VC group / Proportion with the adverse event in control group

Adverse events of special interest

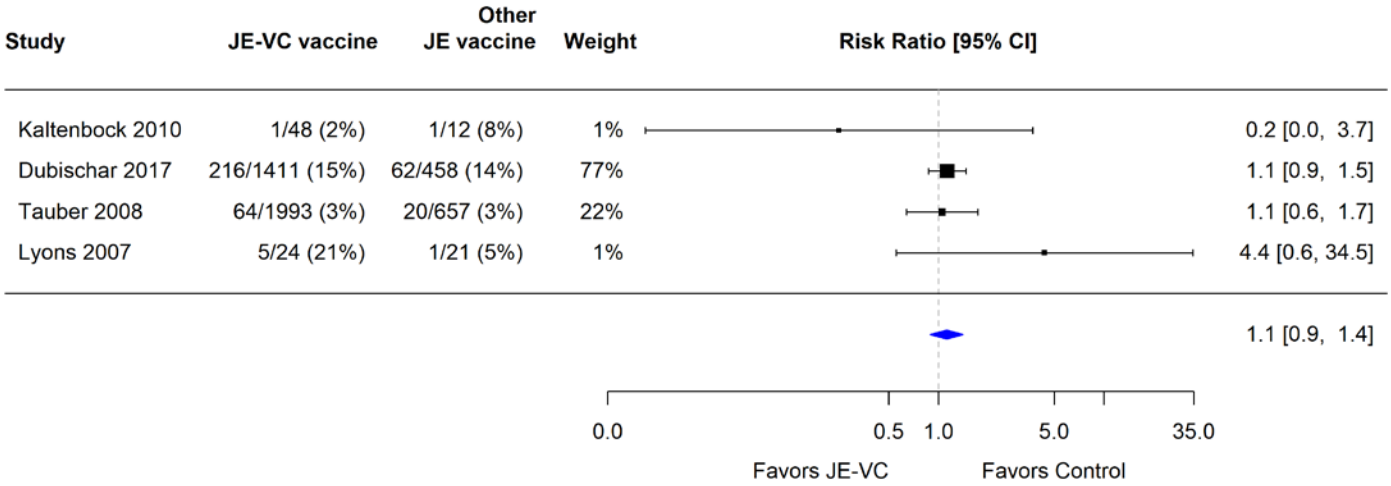
- Fever
- Rash
- Hypersensitivity or urticaria
- Neurologic events
- Medically attended adverse events

Fever reported within 7 days of JE-VC or control vaccine

			Fever*	
Sites	Type	Age (yrs)	JE-VC	Control vaccine
India	RCT	1–2	1/48 (2%)	1/12 (8%)
Philippines	RCT	0.2–17	216/1411 (15%)	62/458 (14%)
US/Eur/Aus	RCT	≥18	64/1993 (3%)	20/657 (3%)
US	RCT	18–49	5/24 (21%)	1/21 (5%)
US/Eur/Aus	Obs	0.2–17	4/100 (4%)	-- --
US	Obs	≥18	6/116 (5%)	-- --
Eur	Obs	64–83	0/200 (0)	-- --

*Definition varies by study ranging from ≥37.6C to ≥38.0C

Pooled risk ratios for fever reported within 7 days of either dose of JE-VC or control vaccine in RCTs*

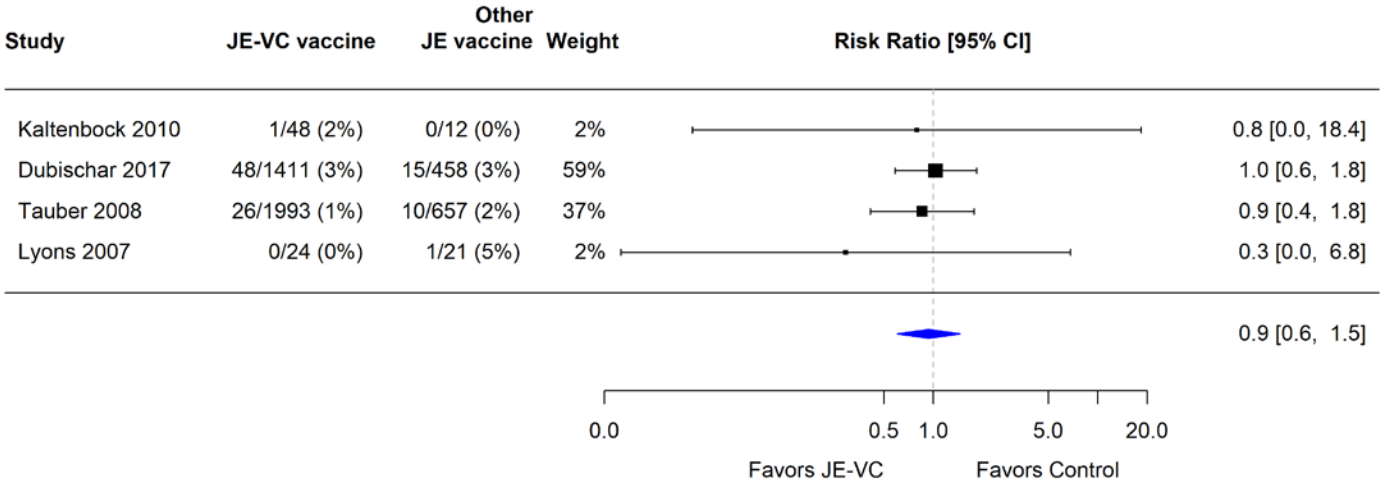


*Risk ratio = Proportion with the adverse event in JE-VC group / Proportion with the adverse event in control group

Rash reported within 7 days of JE-VC or control vaccine

			Rash	
Sites	Type	Age (yrs)	JE-VC	Control vaccine
India	RCT	1–2	1/48 (2%)	0/12 (0)
Philippines	RCT	0.2–17	48/1411 (3%)	15/458 (3%)
US/Eur/Aus	RCT	≥18	26/1993 (1%)	10/657 (2%)
US	RCT	18–49	0/24 (0)	1/21 (5%)
US/Eur/Aus	Obs	0.2–17	4/100 (4%)	-- --
US	Obs	≥18	2/116 (2%)	-- --
Eur	Obs	64–83	0/200 (0)	-- --

Pooled risk ratios for rash reported within 7 days after either dose of JE-VC or control vaccine in RCTs*

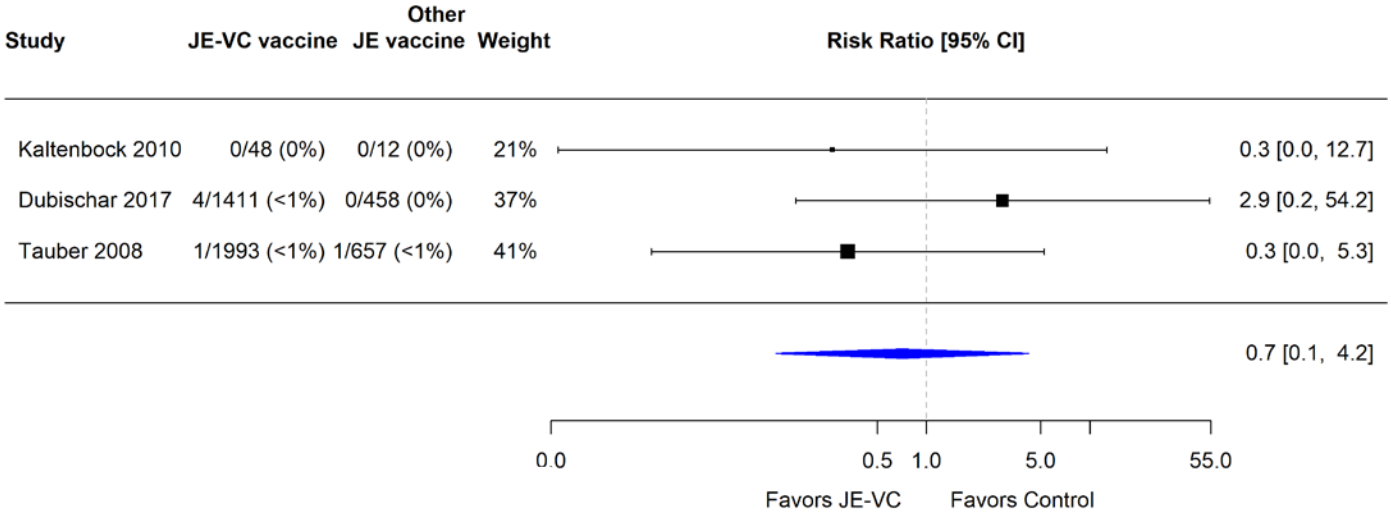


*Risk ratio = Proportion with the adverse event in JE-VC group / Proportion with the adverse event in control group

Hypersensitivity or urticaria reported within 1 month after either dose of JE-VC or control vaccine

			Hypersensitivity or urticaria			
Sites	Type	Age (yrs)	JE-VC		Control vaccine	
India	RCT	1–2	0/48	(0)	0/12	(0)
Philippines	RCT	0.2–17	4/1411	(<1%)	0/458	(0)
US/Eur/Aus	RCT	≥18	1/1993	(<1%)	1/657	(<1%)
US/Eur/Aus	Obs	0.2–17	5/100	(5%)	--	--
US	Obs	≥18	0/116	(0)	--	--
Eur	Obs	64–83	5/200	(3%)	--	--

Pooled risk ratios for hypersensitivity or urticaria within 1 month after either dose of JE-VC or control vaccine in RCTs*



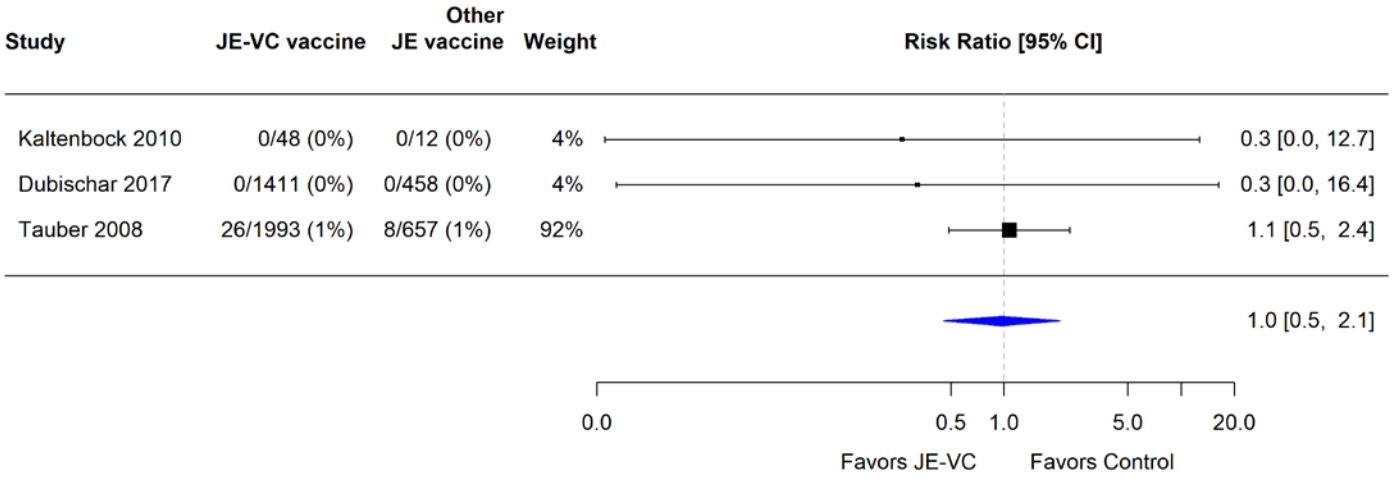
*Risk ratio = Proportion with the adverse event in JE-VC group / Proportion with the adverse event in control group

Neurologic adverse events reported within 1 month after either dose of JE-VC or control vaccine*

			Neurologic adverse events	
Sites	Type	Age (yrs)	JE-VC	Control vaccine
India	RCT	1–2	0/48 (0)	0/12 (0)
Philippines	RCT	0.2–17	0/1411 (0)	0/458 (0)
US/Eur/Aus	RCT	≥18	26/1993 (1%)	8/657 (1%)
US/Eur/Aus	Obs	0.2–17	0/100 (0)	-- --
US	Obs	≥18	0/116 (0)	-- --

*Does not include reports of headache

Pooled risk ratios for neurologic adverse events within 1 month after either dose of JE-VC or control vaccine in RCTs*

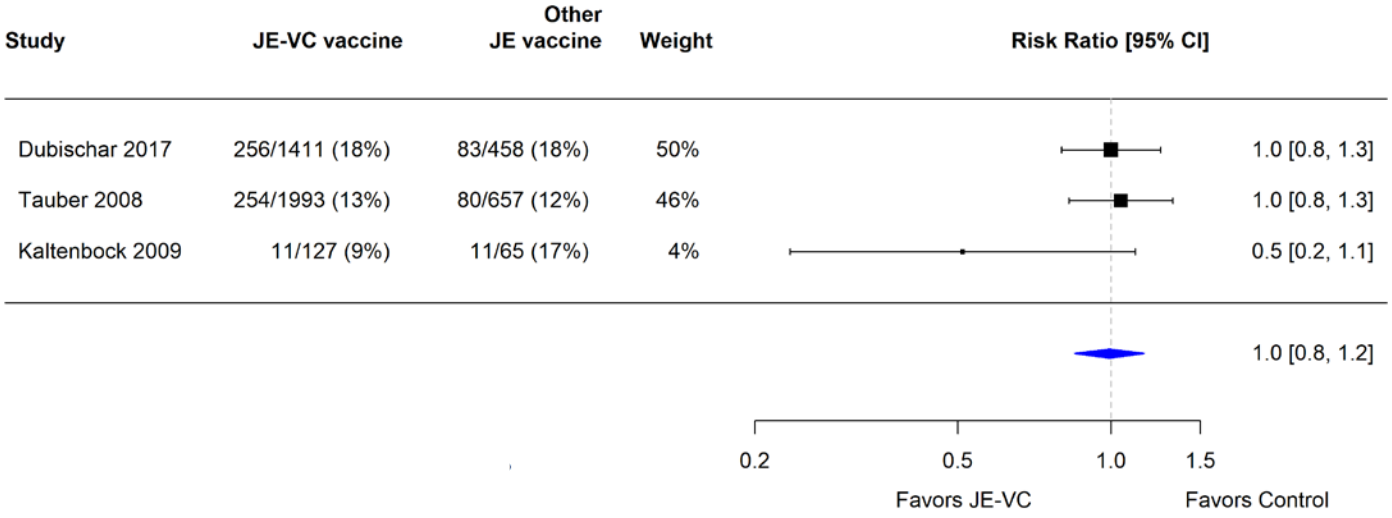


*Risk ratio = Proportion with the adverse event in JE-VC group / Proportion with the adverse event in control group

Medically attended adverse events reported within 1 month after either dose of JE-VC or control vaccine

			Medically attended adverse events	
Sites	Type	Age (yrs)	JE-VC	Control vaccine
Philippines	RCT	0.2–17	256/1411 (18%)	83/458 (18%)
US/Eur/Aus	RCT	≥18	254/1993 (13%)	80/657 (12%)
Eur	RCT	≥18	11/127 (9%)	11/65 (17%)
US/Eur/Aus	Obs	0.2–17	12/100 (12%)	-- --
US	Obs	≥18	0/116 (0)	-- --
Eur	Obs	64–83	38/200 (19%)	-- --

Pooled risk ratios for medically attended adverse events within 1 month after either dose of JE-VC or



*Risk ratio = Proportion with the adverse event in JE-VC group / Proportion with the adverse event in control group

Hypersensitivity reactions reported through post-marketing surveillance

Countries	Reporting period	Doses distributed	Hypersensitivity reactions reported	
			No.	Rate*
US/Eur/Aus	Apr 2009–Mar 2010	246,687	10	4.1
US	May 2009–Apr 2012	275,848	12	4.4
US	May 2012–Apr 2016	802,229	24	3.0
US	Jul 2010–May 2011	36,358	9	24.8

*Per 100,000 doses distributed

Neurologic adverse events reported through post-marketing surveillance*

Countries	Reporting period	Doses distributed	Neurologic reactions reported	
			No.	Rate†
US/Eur/Aus	Apr 2009–Mar 2010	246,687	2	0.8
US	May 2009–Apr 2012	275,848	3	1.1
US	May 2012–Apr 2016	802,229	2	0.2
US	Jul 2010–May 2011	36,358	8	22.0

*Does not include reports of headache
†Per 100,000 doses distributed

Seroprotection, serious adverse events, and events of special interest following receipt of JEEV in children

Outcome	JEEV*		JenceVac¥	
$PRNT_{50}$ titer ≥10 at 1 month	258/280	(92%)	140/142	(99%)
Serious adverse events within 56 days	1/304	(<1%)	1/152	(1%)
Events of special interest within 7 days				
Fever	34/304	(11%)	24/152	(16%)
Rash	4/304	(1%)	2/152	(1%)

*JEEV is manufactured by Biological E (India) with technology transferred from Valneva.

¥Inactivated mouse brain-derived JE vaccine from Korea.

Initial evidence type used for GRADE analysis

1=	RCTs or overwhelming evidence from observational studies
2=	RCTs with important limitations or exceptionally strong evidence from observational studies
3=	Observational studies or RCTs with notable limitations
4=	Clinical experience, observational studies with important limitations, or RCTs with several major limitations

Limitations and evidence type for benefits of JE-VC

	Seroprotection at 1 mo		Seroprotection at 6 mos	
Design (No. studies)	RCT (4)	Obs (8)	RCT (2)	Obs (4)
Risk of bias	No serious	No serious	No serious	No serious
Inconsistency	No serious	No serious	No serious	No serious
Indirectness	No serious	No serious	No serious	No serious
Imprecision	No serious	No serious	No serious	No serious
Evidence type*	1	3	1	3

*Other criteria considered that had no effect on evidence type included publication bias, strength of association, dose response, and residual confounding

Limitations and evidence type for harms of JE-VC

	Serious adverse events		Events of special interest	
Design (No. studies)	RCT (8)	Obs (8)	RCT (5)	Obs (7)
Risk of bias	Yes*	No serious	Yes*	No serious
Inconsistency	No serious	No serious	No serious	No serious
Indirectness	No serious	No serious	No serious	No serious
Imprecision	No serious	No serious	No serious	No serious
Evidence type[¥]	2	3	2	3

*Risk of bias due to inadequate blinding of study participants and personnel.
[¥]Other criteria considered that had no effect on evidence type included publication bias, strength of association, dose response, and residual confounding.

Overall quality of evidence for JE-VC

Outcome	Design (No. studies)	Evidence type	Overall evidence
Seroprotection at 1 mo	RCT (4)	1	1
Seroprotection at 6 mos	RCT (2)	1	
Serious adverse events	RCT (8)	2	2
Events of special interest	RCT (5)	2	

Next steps

- Incorporate information into Evidence to Recommendations Framework (EtR)
- EtR presentation and vote on JE vaccine recommendations at next ACIP meeting

Acknowledgements

- Division of Vector-Borne Diseases
  - Brad Biggerstaff
  - Marc Fischer
  - Kallie Horiuchi

Thank you